

FORM-PTO-1390
(Rev. 12-29-99)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

033265-003

U S APPLICATION NO. (If known, see 37 C.F.R. 1.5)

Unknown 09/936527

INTERNATIONAL APPLICATION NO.
PCT/EP00/02001INTERNATIONAL FILING DATE
March 8, 2000PRIORITY DATE CLAIMED
March 17, 1999TITLE OF INVENTION
CO-CRYSTALLIZATION PROCESSAPPLICANT(S) FOR DO/EO/US
Karl REUTER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form 1449, and reference copies.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: (1) International Search Report; (2) International Preliminary Examination Report; and (3) first page of the International Publication.

U.S. APPLICATION NO. (if known, see 37 CFR 1.50) Unknown 09/936527		INTERNATIONAL APPLICATION NO. PCT/EP00/02001		ATTORNEY'S DOCKET NUMBER 033265-003	
17. <input checked="" type="checkbox"/> The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00 (960) International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 (970) International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 (958) International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 (956) International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 (962)					
ENTER APPROPRIATE BASIC FEE AMOUNT =					
Surcharge of \$130.00 (154) for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)). 20 <input type="checkbox"/> 30 <input type="checkbox"/>				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	19 -20 =	0	X\$18.00 (966)	\$	
Independent Claims	2 -3 =	0	X\$80.00 (964)	\$	
Multiple dependent claim(s) (if applicable)			+\$270.00 (968)	\$	
TOTAL OF ABOVE CALCULATIONS =				\$	860.00
Reduction for 1/2 for filing by small entity, if applicable (see below).				\$	430.00
SUBTOTAL =				\$	430.00
Processing fee of \$130.00 (156) for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)). 20 <input type="checkbox"/> 30 <input type="checkbox"/>				\$	
TOTAL NATIONAL FEE =				\$	430.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 (581) per property +				\$	40.00
TOTAL FEES ENCLOSED =				\$	470.00
				Amount to be:	
				refunded	\$
				charged	\$
<p>a. <input checked="" type="checkbox"/> Small entity status is hereby claimed.</p> <p>b. <input checked="" type="checkbox"/> A check in the amount of \$ <u>470.00</u> to cover the above fees is enclosed.</p> <p>c. <input type="checkbox"/> Please charge my Deposit Account No. <u>02-4800</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>d. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-4800</u>. A duplicate copy of this sheet is enclosed.</p> <p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p>					
<p>SEND ALL CORRESPONDENCE TO:</p> <p>B. Jefferson Boggs, Jr. BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, Virginia 22313-1404 (703) 836-6620</p>					
<p><i>for</i> <u>B. Jefferson Boggs, Jr.</u> SIGNATURE</p> <p><u>32,344</u> REGISTRATION NUMBER</p>					

September 14, 2001

Patent
Attorney Docket No. 033265-003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)	
)	
Karl REUTER)	Group Art Unit: Unassigned
)	
Serial No. Unassigned)	Examiner: Unassigned
(National Stage Filing based on PCT/EP00/02001))	
)	
Filed: September 14, 2001)	
)	
For: CO-CRYSTALLIZATION PROCESS)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please first amend the above-identified application as follows:

IN THE CLAIMS:

Kindly replace Claims 3-6 and 8-10, as follows:

3. (amended) A process according to claim 1 wherein the emulsion is a micro-emulsion.

4. (amended) A process according to claim 1 wherein the emulsion is a macro-emulsion.

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5. (amended) A process accordingly to claim 1, wherein dissolving of additional impure substance in step (e) is carried out by ultrasound, heating and/or stirring.

6. (amended) A process according to claim 1, wherein the crystals isolated in step (d) are washed with water optionally containing surfactant.

8. (amended) A process according to claim 1, wherein crystallization is induced by seeding with seed crystals of the substance.

9. (amended) A process according to claim 1, wherein dissolving of additional impure substance in step (e) is carried out by stirring.

10. (amended) A process according to claim 1, wherein dissolving of additional impure substance in step (e) is carried out by ultrasound and/or heating.

REMARKS

Entry of the foregoing, and consideration of the subject matter of the above-identified application, as amended, are respectfully requested.

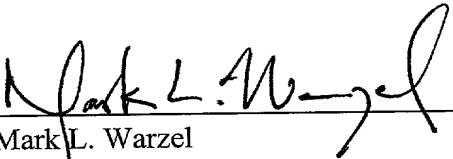
By the foregoing amendment, the claims have been amended to remove multiple dependencies.

Early and favorable consideration on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By:


Mark L. Warzel
Registration No. 47,264

P.O. Box 1404
Alexandria, VA 22313-1404
(703) 836-6620

Date: September 14, 2001

Attachment to Preliminary Amendment filed September 14, 2001

Marked-up Version of Claims 3-6 and 8-10.

Claims 3-6, and 8-10 are amended as follows:

3. (amended) A process according to claim 1 [or 2] wherein the emulsion is a micro-emulsion.
4. (amended) A process according to claim 1 [or 2] wherein the emulsion is a macro-emulsion.
5. (amended) A process accordingly to [any one of the preceding claims] claim 1, wherein dissolving of additional impure substance in step (e) is carried out by [any one or more of] ultrasound, heating [and] and/or stirring.
6. (amended) A process according to [any one of the preceding claims] claim 1, wherein the crystals isolated in step (d) are washed with water optionally containing surfactant.
8. (amended) A process according to [any one of the preceding claims] claim 1, wherein [crystallisation] crystallization is induced by seeding with seed crystals of the substance.
9. (amended) A process according to [any one of the claims 1 to 8] claim 1, wherein dissolving of additional impure substance in step (e) is carried out by stirring.
10. (amended) A process according to [any one of claims 1 to 8] claim 1, wherein dissolving of additional impure substance in step (e) is carried out by ultrasound and/or heating.

Emulsion Crystallisation with RecycleBackground of the Invention

- 5 The present invention relates to a process for purifying an impure substance through emulsion crystallisation. In particular, the present invention enables the preparation of highly purified crystalline materials at high yields.

10 Crystallisation of substances from emulsions is well known. C.f. EP 0 548 028 A1 and WO 97/32644, both belonging to the inventor of the present invention. In such emulsion crystallisation processes, an emulsion is formed of organic liquid droplets in a continuous water phase. Then, a mixture of substances is dissolved in the emulsion, and the emulsion is supersaturated in the desired substance of the mixture. The desired substance is then allowed to crystallise in the water phase, optionally with the aid of seed crystals.

15 The present invention builds upon this technology to enable ultra-high purification of substances at high yields. As such, the present invention vastly increases the commercial potential of emulsion crystallisation processes.

20 The aforementioned patent publications describe emulsion crystallisation processes for purifying substances which optionally can be carried out continuously. In these processes, crystals that are formed are filtered off from the emulsion, and the resulting emulsion-filtrate is heated. The heated emulsion-filtrate is then contacted with impure substance in a column that is kept separate from the vessel in which crystallisation takes place. This serves to re-
25 load the emulsion-filtrate with impure substance, which is then filtered and cooled and re-introduced into the crystallisation vessel.

30 Carrying out emulsion crystallisation continuously, as described in these patent publications, can lead to some difficulties. The equipment it requires is somewhat complicated, requiring the external column, two filters and two heat exchange units. The external column and the filters are susceptible to clogging. The process risks losing emulsion during the removal of undissolved leftover crude materials in the column, which will reduce its efficiency. Re-loading of impure substance in the external column occurs without the benefit of stirring, which also reduces its efficiency.

35 Another disadvantage of some emulsion crystallisation processes is that their yields following a single crystallisation step can be substantially lower than the corresponding yields obtained

by classical crystallisation due to difficulty in removing solvents from the mother liquor. Or the emulsion cannot be highly loaded with impure substance as this would lead to emulsion instability, unworkable viscosity and/or sub-optimal growth conditions for the crystals.

5 Summary of the invention

10 The present invention overcomes the disadvantages of the prior art by providing a simplified method for carrying out emulsion crystallisation with recycle of emulsion. The present invention also provides a method for obtaining substances at ultra-high purity levels and at excellent yields. According to the invention, a process is provided for purifying an impure substance through emulsion crystallisation comprising the steps of (a) forming an emulsion of organic liquid droplets in a continuous water phase, which emulsion contains the impure substance; (b) super-saturating the emulsion in the substance; (c) inducing crystallisation of the substance, whereby crystallisation takes place in the water phase; (d) isolating the crystals of the substance from the emulsion, yielding an emulsion-filtrate; (e) dissolving additional impure substance in the emulsion-filtrate; and (f) repeating steps (b)-(d) with the emulsion obtained from step (e).

15 Detailed Description of the Invention

20 Impure substances to be purified according to the present invention can be any substances that lend themselves to emulsion crystallisation processes. The starting impure substance will typically contain > 60% by weight purity of the substance, preferably >70%, more preferably > 80%. Particularly good results have been found in cases > 95% purity, which have led to final purity of the substance of e.g. > 99.9%.

25 Emulsions and their formation are well-known in the art. Emulsions are, by definition, "droplets" dispersed in a "continuous phase". In the present invention, the droplets are organic liquid droplets and the continuous phase is a water phase.

30 The emulsion optionally contains additives such as surfactants and dispersants, known in the art, for assisting formation and stabilization of the emulsion, and for facilitating the transport of the substance out of the organic liquid droplets and into the water phase, where crystallisation takes place on a crystal surface (i.e. either the seed crystal or spontaneously formed crystal). Such surfactants and dispersants will be chosen according to the nature of the emulsion, and can be nonionic, anionic and/or cationic. The additives will normally be present in an amount of 0.01-30 w/w %, preferably 0.1-20 w/w %.

35

The droplets typically vary in diameter from approximately 0.05 to 80 μm . Droplets with diameter in the range of 0.3 to 80 μm are known as "macrodroplets", and the emulsions as "macroemulsions". Droplets with diameter in the range of 0.05 to 0.3 μm are known as "microdroplets", and the emulsions as "microemulsions". For the sake of simplicity, the terms

5 "droplets" and "emulsions" as used herein encompass both macro- and microdroplets and macro- and microemulsions.

The organic liquid phase of the droplet will be water insoluble. 'Water insoluble' in this context means anything less than water miscible, though in most cases the organic liquid

10 phase will mix with water in an amount not more than 30% w/w at the temperature at which crystallisation takes place.

The emulsion may further contain a buffering agent, such as sodium acetate and acetic acid, for maintaining pH of the emulsion at a desired level, antifreezing agents and solubility

15 adjusting agents, as is known in the art; and may also contain a solubilizer for the impure substance, such as acetone or methanol, which can be easily removed following crystallisation and re-used.

The emulsion can be super-saturated, and crystallisation induced, by any conventional

20 means. Typically, super-saturation will be accomplished by cooling the emulsion. Crystallisation can be initiated either spontaneously, or by seeding with the seed crystals of the substance.

Formation of the original emulsion, as well as re-loading of emulsion-filtrate with impure

25 substance, can be carried out in the vessel in which crystallisation take places, or can be carried out in a separate vessel. This separate vessel will preferably be equipped with stirring, high shear equipment and/or heating means so that an optimum emulsion can be produced.

Isolation of crystals from the emulsion can be carried out by any conventional means, such

30 as filtration or centrifuge. Centrifuging is preferred, since it results in a higher percentage of the emulsion-filtrate being separated from the crystals.

The emulsion-filtrate obtained following isolation of crystals is then 're-loaded' with impure

35 substance, i.e. impure substance is added to it, and dissolved. Dissolving can be carried out by any conventional means, e.g. any one or more of ultrasound, heating and stirring.

Following re-loading and dissolving of the impure substance, the emulsion-filtrate is treated like the original emulsion and is further processed as before, i.e. super-saturated in the substance, crystallisation is induced and the crystals are isolated. Recycling of emulsion-filtrate can be carried out as many times as yields acceptable results. With increasing repetition of recycling of emulsion-filtrate, there is a risk that the purity of crystals isolated will decrease as the level of impurities in the emulsion builds up.

Isolated crystals of substance can be washed as known, e.g. with water, optionally containing surfactants. Applying washing water to the crystals as they are being centrifuged provides a particularly convenient means for carrying out the process.

Representative examples falling within the scope of the present invention but not intended to limit the scope of the present invention follow:

Example 1 – Fluorene

120 g of technical grade fluorene (85% purity) are added to one liter of a micro-emulsion formed from 10% acetophenone, 50% acetone, 10% Synperonic NP 10 (a nonylphenol surfactant, ethoxylated with 10 mol ethyleneoxide; ICI PLC, England) and 30% water. Heating to 95-100 °C dissolves all of the fluorene to provide a clear emulsion. Cooling to room temperature super-saturates the emulsion and yields crystals of fluorene within one hour.

The purified crystals are isolated from the emulsion by centrifuging, and the emulsion-filtrate is set aside. The crystals are washed with a total of 0.5-2 liters of water whilst being centrifuged to remove excess water, and dried at 50-60°C. Alternatively to being washed in the centrifuge, the crystals may be dispersed in water, and this dispersion, then, centrifuged and dried.

The emulsion-filtrate is now re-loaded with 80 g of the same technical grade fluorene, which is then heated at 95-100 °C to dissolve all of the fluorene. The resulting emulsion is treated as before, to yield purified crystals and emulsion-filtrate. This procedure is again repeated so that a total of three crystallisations are carried out. The fluorene crystals produced have a purity on the order of 95%. The total yield obtained from 1 liter emulsion following three crystallisations is 83.5% This compares with a yield of 70.6% following a single crystallisation.

Example 2 - 2,4-Dinitrophenol

140 g of 2,4-dinitrophenol (97% purity) are added to 2 liters of a solution consisting of 2% Soprophor FL (a surfactant), 2% polyvinylalcohol (m.w. 15,000), 2.5% benzonitrile and 93.5% water. The 2,4-dinitrophenol is dissolved, and the solution is emulsified by heating to 90-95 °C and applying ultrasound. Any remaining solids are filtered off. The emulsion is cooled to room temperature over a period of 16 hours, during which 2,4-dinitrophenol crystallises as rectangular plates. These crystals are filtered and washed with 0.5 liters 1% Synperonic NP 10 solution and 1 liter water. The resulting crystals have a purity of > 99.9%.

The emulsion-filtrate is re-loaded with 93.5 g of the 97% 2-4-dinitrophenol and re-emulsified. The emulsion is further treated as described in the previous paragraph. The process is then repeated a third time.

Example 3 – Anthracene

15 g of technical grade anthracene (94.5% purity) are added to 1.5 liters of a micro-emulsion formed from 10% benzonitrile, 50% N-methylpyrrolidinone, 10% Synperonic NP 10 and 30% water. Heating to 95-100 °C dissolves all of the anthracene to provide a clear emulsion. Cooling to room temperature super-saturates the emulsion and yields crystals of anthracene within two hours.

The purified crystals are isolated from the emulsion by centrifuging, and the emulsion-filtrate is set aside. The crystals are washed with a total of 0.5-2 liters of water, centrifuged a second time, and dried at 50-60°C.

The emulsion-filtrate is now re-loaded with 15 g of the same technical grade anthracene, which is then heated at 95-100 °C to dissolve all of the anthracene. The resulting emulsion is treated as before, to yield purified crystals and emulsion-filtrate. This procedure is again repeated so that a total of three crystallisations are carried out. The anthracene crystals produced have a purity on the order of 99.8 %. The total yield obtained from 1.5 liters emulsion following three crystallisations is 86.9% This compares with a yield of 82.1% following a single crystallisation.

Claims:

1. A process for purifying an impure substance through emulsion crystallisation comprising the steps of
 - (a) forming an emulsion of organic liquid droplets in a continuous water phase, which emulsion contains the impure substance;
 - (b) super-saturating the emulsion in the substance;
 - (c) inducing crystallization of the substance, whereby crystallization takes place in the water phase;
 - (d) isolating the crystals of the substance from the emulsion, yielding an emulsion-filtrate;
 - (e) dissolving additional impure substance in the emulsion-filtrate; and
 - (f) repeating steps (b)-(d) with the emulsion obtained from step (e).
2. A process according to claim 1 wherein crystals are isolated from emulsion in step (d) by centrifuge.
3. A process according to claim 1 or 2 wherein the emulsion is a micro-emulsion.
4. A process according to claim 1 or 2 wherein the emulsion is a macro-emulsion.
5. A process according to any one or more of the preceding claims wherein dissolving of additional impure substance in step (e) is carried out by any one or more of ultrasound, heating and stirring.
6. A process according to any one or more of the preceding claims wherein the crystals isolated in step (d) are washed with water optionally containing surfactant.
7. A process according to claim 6 wherein the washing water is applied to the crystals during centrifuging.
8. A process according to any of the preceding claims wherein crystallisation is induced by seeding with seed crystals of the substance.

9. A process according to any one of claims 1 to 8 wherein dissolving of additional impure substance in step (e) is carried out by stirring.
- 5 10. A process according to any one of claims 1 to 8 wherein dissolving of additional impure substance in step (e) is carried out by ultrasound and/or heating.

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T04T60 22592650

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.
033265-003

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

EMULSION CRYSTALLIZATION WITH RECYCLE

the specification of which (check only one item below):

☒ is attached hereto.

☐ was filed as United States application

Number _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/EP00/02001

on March 8, 2000

and was amended

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
PCT	PCT/EP00/02001	08-03-00	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Europe	99200820.1	17-03-99	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.
033265-003

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		
PCT/EP00/02001	March 8, 2000			

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

William L. Mathis	17,337	Eric H. Weisblatt	30,505	Bruce T. Wieder	33,815
Robert S. Swecker	19,885	James W. Peterson	26,057	Todd R. Walters	34,040
Platon N. Mandros	22,124	Teresa Stanek Rea	30,427	Ronni S. Jillions	31,979
Benton S. Duffett, Jr.	22,030	Robert E. Krebs	25,885	Harold R. Brown III	36,341
Norman H. Stepno	22,716	William C. Rowland	30,888	Allen R. Baum	36,086
Ronald L. Grudziecki	24,970	T. Gene Dillahunt	25,423	Brian P. O'Shaughnessy	32,747
Frederick G. Michaud, Jr.	26,003	Patrick C. Keane	32,858	Kenneth B. Leffler	36,075
Alan E. Kopecki	25,813	B. Jefferson Boggs, Jr.	32,344	Fred W. Hathaway	32,236
Regis E. Slutter	26,999	William H. Benz	25,952	Wendi L. Weinstein	34,456
Samuel C. Miller, III	27,360	Peter K. Skiff	31,917	Mary Ann Dillahunt	34,576
Robert G. Mukai	28,531	Richard J. McGrath	29,195		
George A. Hovanec, Jr.	28,223	Matthew L. Schneider	32,814		
James A. LaBarre	28,632	Michael G. Savage	32,596		
E. Joseph Gess	28,510	Gerald F. Swiss	30,113		
R. Danny Huntington	27,903	Charles F. Wieland III	33,096		


21839

and: Mark L. Warzel, Reg. No. 47,264

Address all correspondence to:



21839

B. Jefferson Boggs, Jr.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404

Address all telephone calls to: B. Jefferson Boggs, Jr. at (703) 836-6620.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.
033265-003

FULL NAME OF SOLE OR FIRST INVENTOR Karl REUTER		SIGNATURE <i>Karl Reuter</i>	DATE 28. August 01
RESIDENCE Talstrasse 1, D-79102 Freiburg, Germany		CITIZENSHIP German	
POST OFFICE ADDRESS Talstrasse 1, D-79102 Freiburg, Germany			
FULL NAME OF SECOND JOINT INVENTOR, IF ANY		SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF THIRD JOINT INVENTOR, IF ANY		SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			